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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,579	02/10/2006	Steven Bates	2543-1-046PCT/US	4889
23565	7590	12/15/2006	EXAMINER	
KLAUBER & JACKSON				GANGLE, BRIAN J
411 HACKENSACK AVENUE				PAPER NUMBER
HACKENSACK, NJ 07601				1645

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/537,579	BATES, STEVEN	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 16 October 2006.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-11 and 14-22 is/are pending in the application.
 4a) Of the above claim(s) 4-7,9-11 and 14-22 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-3 and 8 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>9/1/2006</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the response filed 10/16/2006 is acknowledged.

Claims 1-12 and 14-22 are pending. Claims 4-7, 9-10, and 14-22 are withdrawn as being drawn to non-elected inventions. Claims 1-3 and 8 are currently under examination.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on pages 1 and 2. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. It should be noted that the cited occurrences of improper use are only exemplary and applicant should review the specification to correct any other use of embedded hyperlinks and/or other forms of browser-executable code.

Information Disclosure Statement

The information disclosure statement filed 9/1/2005 has been considered. An initialed copy is enclosed.

Claim Objections

Claim 8 is objected to because of the following informalities: the claim is dependent on a non-elected claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The instant claims are drawn to methods of screening or testing for candidate antifungal compounds that impair SEC14 function, using fungal SEC14 that comprises a fragment, a function-conservative variant, an active fragment or a fusion protein of SEC14 (claim2).

The specification disclose a full length SEC14 from an unknown organism with no sequence and no description of how to obtain or make said SEC14. The aforementioned claim encompasses fragments, function-conservative variants, active fragments or fusion proteins of all fungal SEC14. The claim encompasses a vast genus of polypeptides that have no correlation between their structure and function. None of these polypeptides meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that

"applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of full length SEC14, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides with the necessary function, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid and/or protein itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification

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provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2datl966.

Therefore, the claims does not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed is not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115).

Claims 1-3 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The performance of the recited method steps of the claims as drawn would not lead to the stated goals of the claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of

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guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to a method of screening or testing for candidate antifungal compounds that impair SEC14 cytosolic factor enzyme (SEC14) function, comprising: a) providing fungal SEC14; b) providing one or more candidate compounds; c) contacting said SEC14 with said one or more candidate compounds; and d) determining the interaction of the candidate compound with said SEC14 (claim 1); wherein the SEC14 comprises a fragment, a function-conservative variant, an active fragment or a fusion protein of SEC14 (claim 2); wherein the fungal SEC14 is from fungus of *Candida* or *Aspergillus* species (claim 3); and to a method of screening or testing for candidate antifungal compounds that impair SEC14 cytosolic factor enzyme (SEC14) function, comprising: a) providing fungal SEC14 in a eukaryotic cell(s) as defined in claim 4; b) providing one or more candidate compounds; c) contacting said eukaryotic cell(s) with said one or more candidate compounds; and d) determining the interaction of the candidate compound with said SEC14 by assessing the effect on growth or viability of said cells (claim 8).

Breadth of the claims: The claims are broadly drawn in that they encompass any interaction between any fungal SEC14 (for claims 1-2 and 8). The claims encompass any candidate compounds, including any compound that exists or can possibly be created. The claims also encompass fragments, function-conservative variants, active fragments or fusion proteins of SEC14.

Guidance of the specification/The existence of working examples: The specification provides a single working example where (presumably) full-length SEC14 from an unknown

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organism is produced recombinantly in *E. coli* and used in an activity assay which measures the transfer of phosphatidylcholine or phosphatidylinositol using liposomes. The specification does not provide a sequence or description of how to make or obtain said SEC14. The method disclosed in the specification would allow one to determine whether a candidate compound impairs or enhances SEC14 activity, but would not allow one to determine the interaction between the compound and SEC14. The specification is also silent with regard to determining efficacy when "more than one" compound is being tested simultaneously.

State of the art: SEC14 is a well-characterized enzyme. It was originally considered essential for cell viability and Golgi secretory function, at least in *S. cerevisiae* (Lopez *et al.*, J. Cell Biol., 124:113-127, 1994, page 114, column 1, paragraph 2). However, it has since been shown that mutations in at least one of seven genes leads to SEC14-independent secretion and survival, even without SEC14 function (Rudge *et al.*, Genetics, 160:1353-1361, 2002, page 1353, column 1, paragraph 2). In addition, SEC14 is not required for viability or for secretory pathway function in the fungus *Yarrowia lipolytica* (Lopez *et al.*, abstract). While the art has SEC14 activity assays, these utilize liposomes and none determine the interaction, especially *in vivo*, of SEC14 and other compounds.

The claims, as recited, fail to provide the method steps necessary to achieve the stated goals of the claims. The goal of the method is to test antifungal compounds that impair SEC14 function. However, a compound that impairs SEC14 function will not necessarily be an antifungal compound. As shown in the art, SEC14 function is not necessary for cell viability. Some species inherently do not require SEC14, and in others, mutations can allow the use of alternate secretory pathways. In the method of claim 8, one is supposed to assess the viability of eukaryotic cells which are expressing SEC14, after contacting said cells with the candidate compound. First, the claims encompass all eukaryotic cells, not just fungi. One would learn nothing about the antifungal properties of a compound by contacting said compound with an insect or mammalian cell expressing SEC14. Additionally, even in cells which do require SEC14 for viability, if the candidate compound led to cell death, one could not determine that SEC14 was the target of the compound, only that the compound led to cell death.

Moreover, regarding claim 2, the claim encompasses fragments, function-conservative variants, active fragments or fusion proteins of SEC14. These polypeptides encompass a vast

genus of polypeptides that have no correlation between their structure and function. The specification does not disclose which fragments of SEC14 are necessary for a given function (i.e. phosphatidylinositol/phosphatidylcholine transfer). Protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess *et al.* (J. of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar *et al.* (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, fragments of SEC14 that maintained the characteristics of SEC14 could not be predicted. Additionally, Bork (Genome Research, 2000, 10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398,

column 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, column 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, column 3). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, column 2). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399, paragraph bridging columns 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, paragraph bridging cols 1 and 2). Clearly, given not only the teachings of Bowie *et al.*, Lazar *et al.* and Burgess *et al.* but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, it could not be predicted that a fragment or a variant that shares only partial homology with a disclosed protein will function in a given manner (i.e. phosphatidylinositol/phosphatidylcholine transfer). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use the claimed genus of proteins. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-3 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 8 are rendered vague and indefinite by the phrase “determining the interaction of the candidate compound with said SEC14.” It is not clear what constitutes an “interaction”, and, without knowing the interaction, it is not possible to know how to determine said interaction.

Claims 1 and 8 are rendered vague and indefinite by the phrase “method of screening or testing for candidate antifungal compounds.” In order to screen, one would necessarily have to test the compounds. Therefore, it is not clear what limitations are meant to be engendered by said terms.

Claims 1 and 8 are rendered vague and indefinite by the phrase “providing one or more candidate compounds.” If one were to test more than one compound at the same time, as claimed, one would have no way of knowing which compound impaired SEC14 function.

Claim 2 is rendered vague and indefinite by the phrase “wherein the SCE14 comprises a fragment, a function-conservative variant, an active fragment, or a fusion protein of SEC14.” It is not clear what a “function-conservative variant” is, and the term is not defined in the specification. Is there a specific function that must be conserved? What amount of similarity in function is required? Further, if applicant referring to a variant of a fungal SEC14, must the variant be fungal in origin, or are all SEC14 enzymes acceptable? Additionally, claim 2 is broader in scope than its parent claim. Fragments, function-conservative variants, active fragments, and fusion proteins of SEC14 are not encompassed by the term “fungal SEC14” in the parent claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Skinner *et al.* (EMBO J., 12:4775-4784, 1993).

The instant claims are drawn to a method of screening or testing for candidate antifungal compounds that impair SEC14 cytosolic factor enzyme (SEC14) function, comprising: a) providing fungal SEC14; b) providing one or more candidate compounds; c) contacting said SEC14 with said one or more candidate compounds; and d) determining the interaction of the candidate compound with said SEC14 (claim 1); wherein the SEC14 comprises a fragment, a function-conservative variant, an active fragment or a fusion protein of SEC14 (claim 2).

Skinner *et al.* disclose an assay where both wild type SEC14 and a SEC14 fusion protein were contacted with a possible inhibitor and tested for activity (see figure 3).

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Daum *et al.* (Biochimica et Biophysica Acta, 897:240-246, 1986, IDS filed 9/1/2005).

The instant claims are drawn to a method of screening or testing for candidate antifungal compounds that impair SEC14 cytosolic factor enzyme (SEC14) function, comprising: a) providing fungal SEC14; b) providing one or more candidate compounds; c) contacting said SEC14 with said one or more candidate compounds; and d) determining the interaction of the candidate compound with said SEC14 (claim 1); wherein the SEC14 comprises a fragment, a function-conservative variant, an active fragment or a fusion protein of SEC14 (claim 2).

Daum *et al.* disclose an assay where a phosphatidylcholine/phosphatidylinositol transfer protein with a molecular weight of 35 kDa is contacted with several possible inhibitory compounds and tested for activity (see Table 1, Figures 1-2). As SEC14 is a phosphatidylcholine/phosphatidylinositol transfer protein with a molecular weight of 35 kDa, the protein disclosed by Daum *et al.* is deemed to be SEC 14, or at least a function-conservative variant of SEC14, in the absence of evidence to the contrary.

Claims 1-2 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Bankaitis *et al.* (J. Cell. Biol., 108:1271-1281, 1989).

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The instant claims are drawn to a method of screening or testing for candidate antifungal compounds that impair SEC14 cytosolic factor enzyme (SEC14) function, comprising: a) providing fungal SEC14; b) providing one or more candidate compounds; c) contacting said SEC14 with said one or more candidate compounds; and d) determining the interaction of the candidate compound with said SEC14 (claim 1); wherein the SEC14 comprises a fragment, a function-conservative variant, an active fragment or a fusion protein of SEC14 (claim 2); and to a method of screening or testing for candidate antifungal compounds that impair SEC14 cytosolic factor enzyme (SEC14) function, comprising: a) providing fungal SEC14 in a eukaryotic cell(s) as defined in claim 4; b) providing one or more candidate compounds; c) contacting said eukaryotic cell(s) with said one or more candidate compounds; and d) determining the interaction of the candidate compound with said SEC14 by assessing the effect on growth or viability of said cells (claim 8).

Bankaitis *et al.* disclose a method where *S. cerevisiae* cells were transformed with SEC14 and fusion proteins of SEC14. These cells were exposed to compounds which might inhibit SEC14, and were then tested for viability (see paragraph bridging page 1273 and 1274).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brian Gangle

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ROBERT A. ZEMAN
PATENT EXAMINER